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Peripheral cytokine levels and response to antidepressant treatment in depression: a systematic review and meta-analysis

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ABSTRACT

Predicting antidepressant treatment response has been a clinical challenge for major depressive disorder (MDD). The inflammation hypothesis of depression suggests that cytokines play a key role in the pathophysiology of MDD and alterations in peripheral cytokine levels are associated with antidepressant treatment outcome. Present meta-analysis aimed to examine the association between baseline peripheral cytokine levels and the response to antidepressant treatment and to evaluate whether changes of cytokine levels were associated with the response to antidepressant treatment in patients with MDD. Human-based studies published in any language in peer-reviewed journals were systematically searched from the PubMed, Embase and Web of Science databases, from inception up to October 2018. The search terms included cytokine, depressive disorder and antidepressant and their synonyms. Case-control or case-case studies reporting on levels of IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, CRP, TNF-α, IFN-γ, GM-CSF, MIP-1α and Eotaxin-1 in patients with MDD based on validated depression scales both before and after antidepressant treatment were included. Of 7408 identified records, 44 studies met inclusion. Standardized mean differences in each cytokine were evaluated and random-effects meta-analyses were performed. MDD patients who responded to antidepressant treatment had lower baseline IL-8 levels than the non-responders (Hedge's g = -0.28; 95% CI, -0.43 to -0.13; P = 0.0003; FDR = 0.004). Antidepressant treatment significantly decreased levels of TNF-α (Hedge's g = 0.60; 95% CI, 0.26 to 0.94; *P* = 0.0006; FDR = 0.004) only in responders and responders showed significantly more decreased TNF-α levels compared to non-responders (*P* = 0.046). These findings suggested that alterations in peripheral cytokine levels were associated with antidepressant treatment outcomes in MDD. Further investigations are warranted to elucidate sources of heterogeneity and examine the potentiality of using inflammatory cytokines as novel predictive markers for the pharmacological treatment of MDD.

Introduction

Major depressive disorder (MDD) is the most prevalent psychiatric disorder with an estimated life-time prevalence of 10-20% [1]. Second-generation antidepressants, e.g. selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), are the most commonly used pharmacological treatments for MDD, however only ~30% of the patients achieve remission with the first prescribed antidepressant [2]. A challenge in treating MDD is the heterogeneity among patient response.

The monoaminergic theory has been the dominant hypothesis of MDD, and most antidepressants are considered to primarily modulate monoaminergic neurotransmission. However, emerging evidence has suggested that aberrant inflammatory processes are involved in the development of MDD and also in mediating the response to antidepressant treatment [3, 4]. Cytokines are key messengers between immune cells, mediating the initiation and cascade of inflammatory response and can have both pro- and anti-inflammatory properties [4, 5]. The cytokine hypothesis of depression posits that cytokines play a key role in the pathophysiology of MDD [4, 5]. Much attention has been devoted to the study of interleukin-1β (IL-1β), IL-6 and tumor necrosis factor α (TNF-α), which have been found to be elevated in serum/plasma and cerebrospinal fluid of depressed patients in the absence of comorbid somatic diseases [6]. Anti-inflammatory cytokines, such as IL-4 and IL-10, were shown to have lower levels in depressed individuals [7, 8]. Antidepressant treatments also influence inflammatory processes, specifically reduction of peripheral IL-6, IL-10, TNF-α and the monocyte chemoattractant protein 1 (MCP1) were reported in MDD patients after antidepressant treatment in recent meta-analyses [9]. However, by evaluating the MDD patients as a whole group, those studies cannot differentiate the reduction in cytokine levels between patients who are antidepressant responders and non-responders. Studies have suggested that decrease in certain cytokine levels, e.g. TNF-α, were seen only in SSRI responders [10, 11]. Interestingly, baseline cytokine levels have been reported to be involved in the response to antidepressant treatment. For example, higher levels of IL-6 were associated with treatment refractory depression [11].

The association between MDD and disturbed peripheral cytokine levels has been examined in various meta-analyses [6, 12], however very few meta-analyses have evaluated the association between baseline cytokine levels and treatment response. Strawbridge et al conducted the first such meta-analysis, however due to the limited number of studies available at that time, only three cytokines (IL-6, TNF-α and CRP) were subject to small meta-analyses from which no clear picture emerged [13]. These reported effects should be interpreted with caution because of possible publication bias. With emerging studies investigating the effect of inflammatory cytokine levels on antidepressant treatment, it is important to perform an updated, methodologically rigorous meta-analysis on the association between peripheral cytokine levels and response to antidepressant treatment in MDD.

Materials and Methods

Inclusion criteria

Records were screened regarding the following inclusionary criteria: 1) adult patients suffering from any depressive disorder (i.e., MDD, persistent depressive disorder) diagnosed according to the international diagnosis tools, e.g. Diagnostic and Statistical Manual of Mental Disorders (DSM), or the International Classification of Diseases (ICD); 2) any kind of pre-treatment assessment of inflammatory cytokine/chemokine, including IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, CRP, TNF-α, IFN-γ, granulocyte-macrophage colony-stimulating factor (GM-CSF), MIP-1α (a.k.a CCL3) or Eotaxin-1 (a.k.a. CCL11); 3) treatment including at least 4 weeks of continuous administration of any antidepressant; 4) standardized post-treatment symptom measure with a reported cut-off value dividing patients into non-responders and responders. Exclusive criteria include: 1) Studies conducted in bipolar patients, unless separate data for unipolar patients could be extracted; 2) Studies which included a psychological or physiological stressor, or anti-inflammatory treatment either by a targeted agent or by specific immunomodulatory drugs (e.g. non-steroidal anti-inflammatory drugs were excluded, but not psychotropic medications).

Search strategy

A systematic search was conducted in the PubMed, Embase, and Web of Science databases from inception up to October 2018 (JJL and YBW). Key words and subject headings were combined in accordance with the thesaurus of each database. The search string consisted of three components all of which were required: 1) "cytokine" and synonyms, including its components (e.g., IL-1); 2) "depressive disorder" and synonyms; and 3) "antidepressant" and synonyms. All the included studies were conducted in humans and written in English. The details of the strategy are available in the **Supplementary Table 1**.

Data extraction

We extracted the means, standard deviation (SD) and sample sizes for both responders and non-responders in addition to methodological and participant characteristics. In studies that provided log-transformed values, the raw scale was transformed based on Higgins et al's method one [14]. In studies that provided comparison results between responders and non-responders, or before and after treatments, measures of *z*-score, *t*-score and *P*-values were extracted. If the data were missing from the original study, we contacted the corresponding authors. Data was also extracted from bar chart using Engauge Digitizer when the authors could not provide the original data [15].

Quality assessment of included studies

We referred to the New-castle-Ottawa scale for observational studies [16], together with Cochrane common classification scheme for bias, and adapted a quality tool containing following parameters to assess the methodological quality of included studies: 1) Was the sample size ≥ 40 at baseline (Yes = 1, No = 0); 2)

Whether the severity of depression were reported at baseline (Yes = 1, No = 0); 3) Whether potential confounders were assessed for both responders and non-responders (age, gender, smoking, body mass index, and time of blood draw) (for each confounder: Yes = 1, No = 0; the maximum of this parameter is 5); 4) Whether the patients were drug-naïve or experienced a washout period (Yes = 1, No = 0); 5)

Whether the attrition rate ≤ 20% (Yes = 1, No = 0); 6) Whether we used data approximation or data extraction software (Yes = 0, No = 1); 7) Whether the manufacturer or parameters of the test were reported (Yes = 1, No = 0). Accordingly, the total score may vary from 0 to 11, with a higher score indicating a higher research quality.

Statistical analysis

Meta-analyses were conducted only when each cytokine was investigated with at least three individual datasets. Standardized mean difference and 95% CI were estimated for each cytokine, providing an unbiased effect size (ES) [17]. Heterogeneity across studies was assessed using the Cochran Q test and was quantified with the I^2 statistic [18]. $I^2 < 25\%$ was deemed to have low heterogeneity, 25% to 75%, medium heterogeneity and $I^2 \geq 75\%$ high heterogeneity. We anticipated a high degree of heterogeneity therefore pooled ES using a random-effects model. An ES of 0.2 was considered low, 0.5 moderate, and 0.8 large [19]. Sensitivity analyses were performed for statistically significant ES estimates by excluding one study from analyses at a time to verify whether a single study turned results non-significant or otherwise changed the direction of the ES. Publication bias was inspected using funnel plot for asymmetry and examined using Egger's test. A P-value < 0.05 was considered the presence of small-study effect [20]. The trim-and-fill test was used to estimate the ES adjusting for publication bias [21]. To further investigate sources of heterogeneity across studies, subgroup or random-effects meta-regression analyses were conducted. The potential confounders were considered: sex (%), age, sample type (serum/plasma), medication status on study-entry, length of treatment, cytokine detection methods (ELISA or other), study quality, publication year, the source of the patients (inpatient/outpatient/mixed). All analyses were performed using R [22] metafor package [23]. P value ≤ 0.05 was considered statistically significant.

Results

Characteristics of included studies

In total, 7408 potentially eligible studies were identified, of which 44 original studies met the inclusion criteria and were included in our meta-analysis (**Figure 1, Supplementary Table 2**). All studies were in longitudinal design, measuring the inflammatory cytokines pre- and post-treatment. Most studies dichotomized patients into responders and non-responders at the end of the study based on a ≥ 50% reduction of the score from the selected depression severity rating scale. Eight studies considered all patients to be responders [8, 24-30]. Forty-two studies were able to provide data of response to exclusively pharmacological treatment and two studies provided the cytokine values by combining both pharmacological and non-pharmacological treatments [24, 31]. Three studies pre-selected treatment-resistant patients to study the effect of augmentation treatments [32-34].

Baseline inflammatory cytokine levels and its association with antidepressant treatment response

IL-8 levels were investigated in nine studies comprising 397 responders and 311 non-responders. MDD patients who showed better treatment response at the endpoint had significantly lower baseline IL-8 levels compared to the non-responders, with a moderate ES (Hedge's g = -0.28, P = 0.0003, FDR = 0.004, **Table 1**, **Figure 2a,** [32, 33, 35-41]). Neither small-study effect (Egger's test for publication bias: P = 0.20) nor heterogeneity was observed (Q = 3.44, P = 0.90; I^2 = 0). In sensitivity analysis, the exclusion of any single study one-at-a-time did not alter the direction or statistical significance of the ES.

CRP levels were numerically lower in those who subsequently became responders, though the difference between responders and non-responders was not statistically significant (Hedge's g = -0.13, P = 0.07, **Table 1**, **Figure 2b,** [11, 31, 34, 37, 38, 42-48]). No small-study effect was observed (Egger's test: P = 0.87) and the heterogeneity was small (Q = 20.47, P = 0.04; I^2 = 15.59). Subgroup analyses showed that studies recruiting inpatient subjects were associated with lower heterogeneity compared to studies with outpatient patient source (**Supplementary Table 3**).

Baseline IL-6 levels did not significantly differ between responders (n = 565) and non-responders (n = 561) across 19 included studies (Hedge's g = -0.91, P = 0.36, **Figure 2c,** [10, 11, 31, 33-38, 41, 42, 49-57]). No small-

study effects were observed (Egger's test: $P = 0.10$). The ES remained insignificant after adjustment for publication bias. The heterogeneity was large ($I^2 = 97.49\%$). Subgroup analyses suggested that using ELISA-based detection method, plasma sample type and inpatient subject source were associated with higher heterogeneity between studies, compared to other types of assay (e.g. multiplex beads array or flow cytometry etc), serum sample type and outpatient/mixed patient source, respectively (**Supplementary Table 3**). Meta-regression did not identify any significant study-specific covariate that could explain the heterogeneity (**Supplementary Table 4**).

No differences of baseline IL-1β, IL-2, IL-4, IL-5, IL-10, IL-12 TNF-α, IFN-γ, GM-CSF, MIP-1α and Eotaxin-1 levels were found between patients who were subsequent responders and non-responders (all $P > 0.05$). The forest plots for these estimates were provided in **Supplementary Figure 1-11**. The comparisons of log-scale transformed data were provided in **Supplementary Table 5**.

Effects of treatment and outcome of treatment response

Levels of TNF-α were significantly decreased after antidepressant treatment only in responders with a moderate ES (Hedge's g = 0.60, $P = 0.0006$, FDR = 0.004, **Table 2, Figure 3a,** [8, 10, 11, 24-26, 32, 33, 35-42, 44, 46, 49, 50, 52, 56, 58-63]) but not in non-responders (Hedge's g = 0.14, $P = 0.18$, **Supplementary Figure 12**). In responders, there was evidence of small-study effects (Egger's test: $P = 0.03$). The ES did not change after adjustment for publication bias. The heterogeneity in the responder group was large ($Q = 221.78$, $P < 0.001$; $I^2 = 90.98\%$). Subgroup analyses suggested that the measurement of TNF-α with ELISA method was associated with higher heterogeneity compared to other types of assay (**Supplementary Table 6)**. Meta-regression analysis showed that the reduction of TNF-α levels in responders was significantly negatively correlated with ELISA based methods (**Supplementary Table 7**). Sensitivity analysis showed that the exclusion of any single study one-at-a-time did not alter the direction or statistical significance of the ES. We also compared the changes of TNF-α levels (ΔTNF-α = endpoint - baseline) between responders and non-responders and found that after antidepressant treatment responders had significantly more decreased TNF-α levels compared to non-responders ($P = 0.046$).

Levels of IL-5 were significantly reduced after antidepressant treatment only in responders with a moderate ES (Hedge's g = 0.67, $P < 0.0001$, FDR = 0.0014, **Table 2**, **Figure 3b,** [36, 37, 44]) but only nominally significant in non-responders (Hedge's g = 0.65, $P = 0.04$, FDR = 0.56, **Supplementary Figure 13**). There was no evidence of publication bias in both groups but the heterogeneity was large in non-responders ($Q = 6.34$, $P = 0.04$, $I^2 = 80.71\%$). Sensitivity analysis showed that the exclusion of any single study one-at-a-time did not alter the direction or statistical significance of the ES in responders. No significant difference in changes of IL-5 (ΔIL-5) levels were found between responders and non-responders.

Levels of GM-CSF were significantly decreased after antidepressant treatment only in responders with a moderate ES (Hedge's g = 0.33, $P = 0.007$, FDR = 0.03, **Table 2**, **Figure 3c,** [33, 36, 44]) but not in non-responders (Hedge's g = 0.16, $P = 0.47$, **Supplementary Figure 14**). In the responders, there was no evidence of publication bias (Egger's test: $P = 0.75$) or significant heterogeneity ($Q = 3.86$, $P = 0.28$, $I^2 = 3.58\%$). Sensitivity analysis showed that the exclusion of two of the three studies one-at-a-time changed the statistical significance of the ES. No significant difference in changes of GM-CSF (ΔGM-CSF) levels were found between responders and non-responders.

No significant treatment effects were observed on levels of IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IFN-γ, CRP, MIP-1α, and Eotaxin-1 in either responders or non-responders (all $P > 0.05$, **Supplementary Figure 15-36**). The log scaled data comparison was provided in **Supplementary Table 8**.

Discussion

This meta-analysis investigated the relationship between peripheral cytokines levels and response to antidepressants treatment in depression. Our results suggested that MDD patients who showed better response to antidepressant treatment had lower baseline IL-8 levels compared to the non-responders, while antidepressant treatment significantly decreased TNF-α, IL-5 and GM-CSF levels only in responders.

Our meta-analysis for the first-time suggested IL-8 was associated with antidepressant treatment response in MDD. IL-8 is a well-documented chemotactic factor for the recruitment of neutrophils to the sites of infection and damage [64]. Later it was shown to activate neutrophil function and may serve as a secondary mediator of inflammation. In peripheral tissues, IL-8 can be secreted by monocytes, lymphocytes and endothelia, and can infiltrate neutrophils through the blood-brain barrier [64-66]. In the central nervous system (CNS), activated microglia is the main secretory source of IL-8 and expresses CXCR2 receptor for the chemokine, providing a positive feedback mechanism for a sustained amplification of inflammatory response [67]. However, the detailed functions of IL-8 are still not clear. IL-8 may play both pro- or anti-inflammatory roles depending on the concentration, which may in part explain the inconsistent association between IL-8 levels and depression. For example, high circulating levels of IL-8 have been shown to decrease the infiltration of neutrophils to the inflammatory site [68]. A recent study reported higher baseline IL-8 levels predict poor antidepressant response in bipolar disorder [69], suggesting antidepressant response may share common mechanisms between MDD and bipolar depression. We should mention that we can not exclude the possibility that the association between a lower baseline IL-8 level and better antidepressant treatment outcome is due to the improvement in patients' depressive symptoms over time, since very few studies have examined the levels of inflammatory cytokines in a control group both at baseline and endpoint.

Compared to Strawbridge et al's study, more cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, MIP-1α, Eotaxin-1 and IFNγ) were included in our study which complemented the results of previous study. Kohler and colleagues [70] performed currently the most comprehensive meta-analysis in the field and it is one of the landmark studies investigating peripheral alterations in cytokine and chemokine levels after antidepressant treatment in major depressive disorder. Based on Kohler et al's study, we complemented the evaluation of the association between levels of baseline cytokine and response to antidepressant treatment and we hypothesized that responders and non-responders may change differently in cytokine levels in response to the treatment. Therefore, the search strategy was different between the

two studies resulting in different studies included in the analysis. The primary focus of Kohler et al's study was to investigate the changes of cytokine levels before and after antidepressant treatment in all depression patients while we focused on the changes in responders and non-responders separately. Several cytokines, including TNF-α and IL-10, were reported in their study to be decreased after antidepressant treatment, however the results should be cautiously interpreted because the changes may only be a reflection from the responders. The maintenance of heightened cytokine levels, e.g. TNF-α, possibly underscores a lack of clinical improvement from the non-responders. Consistently, we found levels of TNF-α were decreased only in responders and responders had significantly more decreased TNF-α levels (ΔTNF-α) compared to non-responders. Although antidepressants may decrease TNF-α levels, we should note that both our study and previous meta-analyses have found a high degree of heterogeneity across studies, suggesting TNF-α levels may be sensitive to outside signals thus subject to dynamic changes [13, 70]. Antidepressants have been shown to have anti-inflammatory effects both in peripheral immune cells and microglia in the CNS, the latter being the main cells responsible for inflammatory process in the brain [71-73]. Peripheral cytokines can also exert effects on CNS by entering the brain through volume diffusion or via active cytokine transporters at the blood-brain barrier [67].

The mechanism underlying antidepressant response is complicated and much of what is known came from pharmacogenetic studies. Interestingly, some genetic markers that survived genome-wide association significance were reported to locate in genes involved in inflammatory process. E.g. studies from GENDEP cohort reported markers in *IL-11* gene and on a lower level of significance, *IL-6* [74], which support the role of inflammatory pathways in antidepressants efficacy. IL-5 gene is located on human chromosome 5, which is in close proximity to the genes encoding for GM-CSF, IL-3 and IL-4. We found antidepressant decreased IL-5 and GM-CSF levels only in responders, suggesting the responders may have different genetic background compared to the non-responders and that these two genes may be modulated by the same genetic loci in responders. We should note that the results of decreased IL-5 and GM-CSF levels in responders were generated from only 3 studies, providing limited power to draw a

definite conclusion. Besides, we did not find significant difference in changes of IL-5 (ΔIL-5) and GM-CSF (ΔGM-CSF) levels between responders and non-responders. IL-10 is considered an anti-inflammatory cytokine, however we found that it had a decreased trend after antidepressant treatment in responders. We speculate that both IL-5 and IL-10 belong to the T helper 2 (Th2)-derived cytokines, therefore may share common pathways that can be affected by antidepressant treatment. Similarly, previous reports have shown that long-term treatment with SSRIs increased Th1-derived cytokines (e.g. IL-1β, IL-2, and IFNγ) while decreased Th2-derived cytokines (IL-4, IL-5, IL-6 and IL-10) [75].

There are several limitations in our study. We only searched three widely used database, nevertheless, the search strategy was carefully developed as all the relevant studies were identified and no study was added by manual search. Conference papers were included if data were available after we contacted with the authors. Future progress will be facilitated by the comprehensive concern of all the possible gray literature. Due to the small number of studies included in each analysis, we should mention that we could not exclude the possibility of publication bias and small study-effects even though Egger's test has been performed. The methodological quality of included studies varied significantly. The quality assessment showed that many of the original studies were at moderate to high risk of bias. Eighteen in forty-four studies had a sample size lower than 40. We only dichotomized the patients into responders and non-responders due to the difficulty to retrieve depressive severity data that measured as a continuous outcome, which may limit our statistical power in the analysis. Similarly, we were unable to get enough data to control variables such as smoking status and body mass index, which may affect cytokine levels. Future studies will benefit from the strict study design and increased sample size. There was substantial heterogeneity across studies, which may be only partially explained by meta-regression analyses, thus the results should be interpreted with caution. Although all studies included pharmacological treatment, the mechanisms of action varied between different drugs, limiting the conclusiveness of our findings. Two studies included non-pharmacological treatment which may present alternative mechanisms of cytokine action, thus weaken the associations we observed.

Conclusion remark

Our study is to date the most comprehensive meta-analysis investigating the association of levels of circulating cytokines and antidepressant treatment response. Although so many cytokines have been investigated by researchers, our meta-analysis demonstrated that most of the associations were not significant. Our results showed that MDD patients with lower baseline circulating IL-8 levels were associated with better response to antidepressant treatment, suggesting levels of IL-8 may be useful for identifying subjects that will fail to respond to current antidepressant therapies and for determining novel treatment strategy. The mechanisms of IL-8 in antidepressant response in CNS warrants further studies, e.g. induced pluripotent stem cell technology can be used as an *in vitro* model. In addition to measuring circulating IL-8 levels, genetic polymorphisms in IL-8 and genes interact with or involved in IL-8 pathways are also potential candidates that can predict treatment response, which warrants future investigations.

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Conflict of interest

None.

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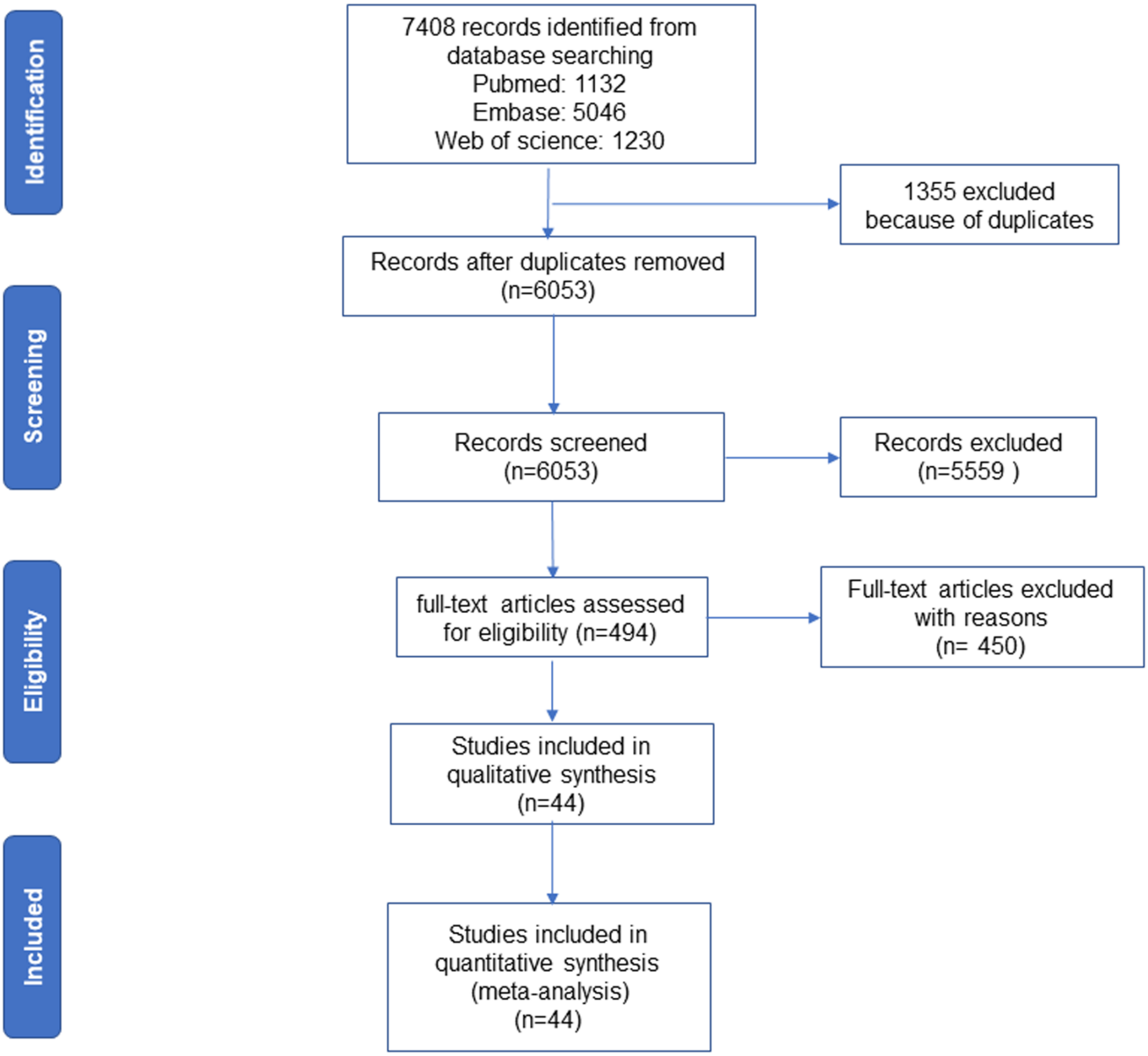
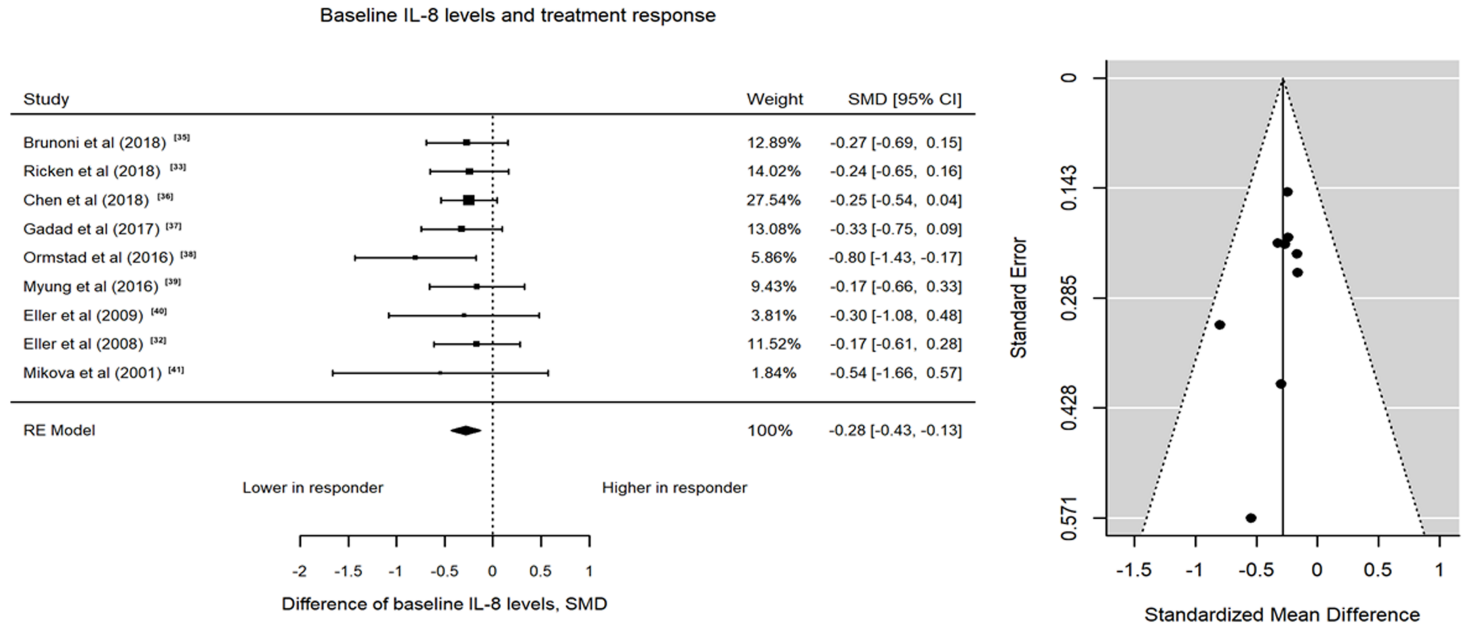
Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection.

Figure 2. MDD patients who showed better treatment response at the endpoint had significantly lower baseline **2a**) IL-8 levels compared to the non-responders. Although **2b**) CRP and **2c**) IL-6 were numerically lower in the responders, the difference was not statically significant from non-responder patients. Each square shows the effect size for a single study, with the horizontal line running through each square demonstrating the width of the 95% CI. The size of the square is proportional to the weight attributed to each study. The diamond represents the summary effect size with the middle equaling the summary effect size and the width depicting the width of the overall 95% CI.

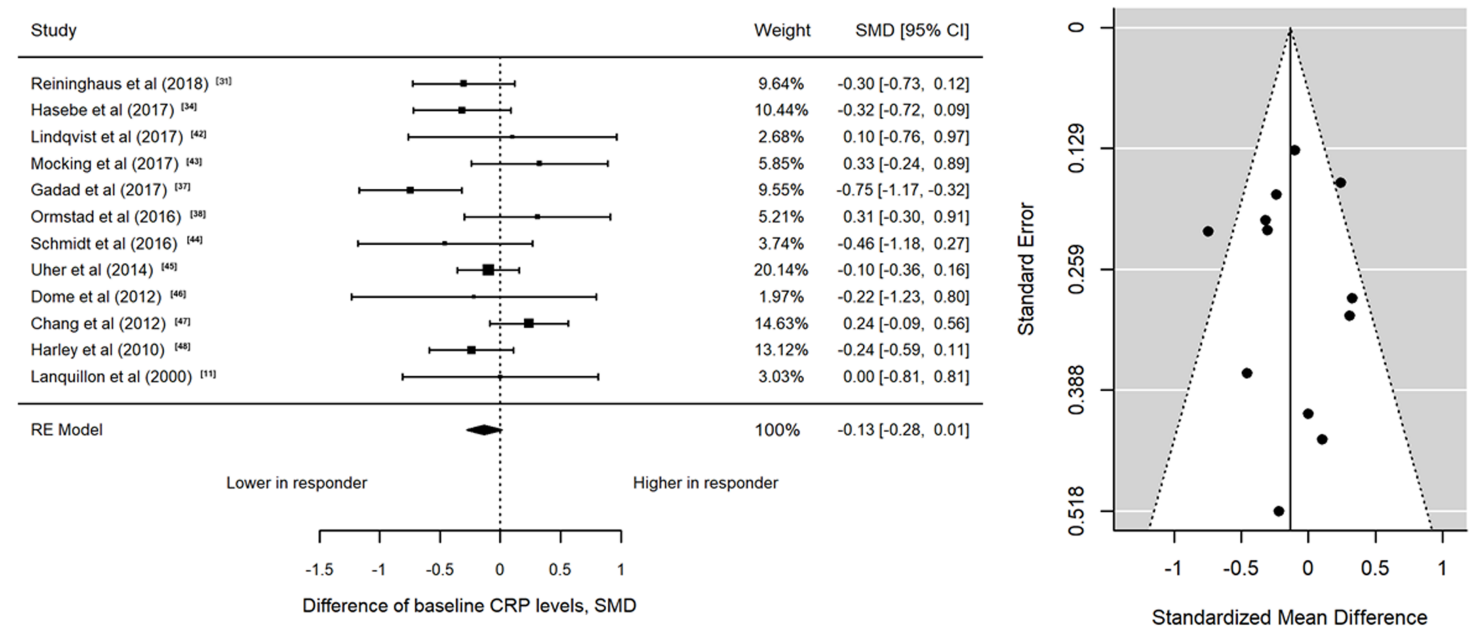
Figure 3. Antidepressant treatment significantly decreased levels of **3a**) TNF-α, **3b**) IL-5, **3c**) GM-CSF only in treatment responders, but not in non-responders. Each square shows the effect size for a single study, with the horizontal line running through each square demonstrating the width of the 95% CI. The size of the square is proportional to the weight attributed to each study. The diamond represents the summary effect size with the middle equaling the summary effect size and the width depicting the width of the overall 95% CI.


Identification
Screening
Eligibility
Included
7408 records identified from database searching
Pubmed: 1132
Embase: 5046
Web of science: 1230
1355 excluded because of duplicates
Records after duplicates removed (n=6053)
Records screened (n=6053)
Records excluded (n=5559)
full-text articles assessed for eligibility (n=494)
Full-text articles excluded with reasons (n= 450)
Studies included in qualitative synthesis (n=44)
Studies included in quantitative synthesis (meta-analysis) (n=44)

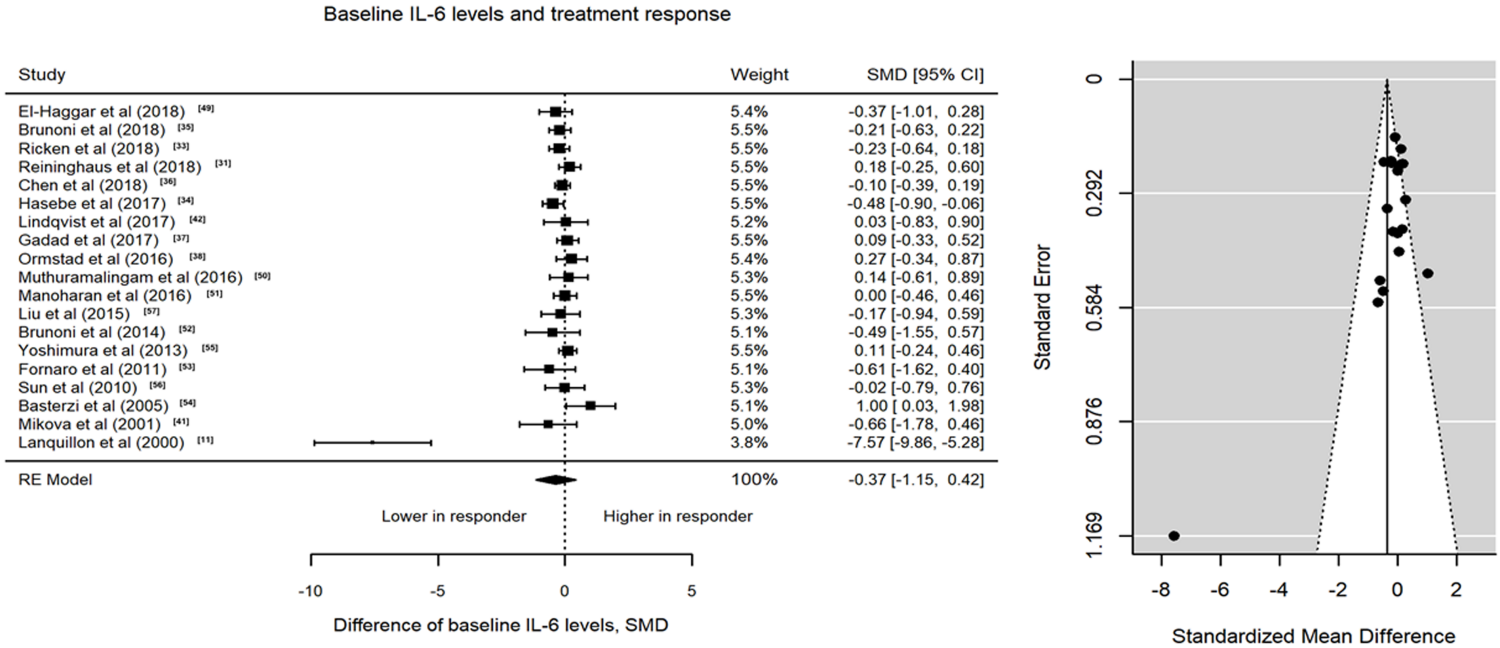
a


Baseline IL-8 levels and treatment response
Study
Weight
SMD [95% CI]
Brunoni et al (2018) [35] 12.89% -0.27 [-0.69, 0.15]
Ricken et al (2018) [33] 14.02% -0.24 [-0.65, 0.16]
Chen et al (2018) [36] 27.54% -0.25 [-0.54, 0.04]
Gadad et al (2017) [37] 13.08% -0.33 [-0.75, 0.09]
Ormstad et al (2016) [38] 5.86% -0.80 [-1.43, -0.17]
Myung et al (2016) [39] 9.43% -0.17 [-0.66, 0.33]
Eller et al (2009) [40] 3.81% -0.30 [-1.08, 0.48]
Eller et al (2008) [32] 11.52% -0.17 [-0.61, 0.28]
Mikova et al (2001) [41] 1.84% -0.54 [-1.66, 0.57]
RE Model 100% -0.28 [-0.43, -0.13]
Lower in responder
Higher in responder
-2 -1.5 -1 -0.5 0 0.5 1
Difference of baseline IL-8 levels, SMD
Standard Error
0 0.143 0.285 0.428 0.571
-1.5 -1 -0.5 0 0.5 1
Standardized Mean Difference

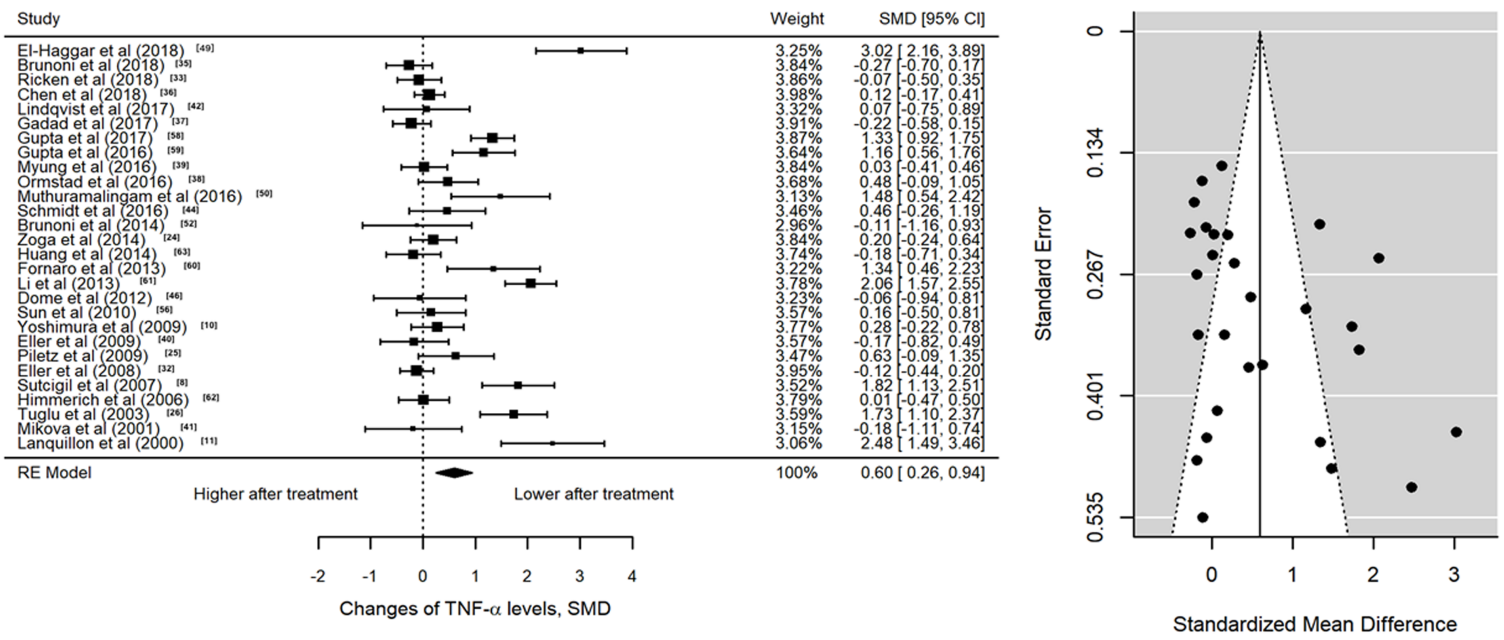
b


Baseline CRP levels and treatment response
Study
Weight
SMD [95% CI]
Reininghaus et al (2018) [31] 9.64% -0.30 [-0.73, 0.12]
Hasebe et al (2017) [34] 10.44% -0.32 [-0.72, 0.09]
Lindqvist et al (2017) [42] 2.68% 0.10 [-0.76, 0.97]
Mocking et al (2017) [43] 5.85% 0.33 [-0.24, 0.89]
Gadad et al (2017) [37] 9.55% -0.75 [-1.17, -0.32]
Ormstad et al (2016) [38] 5.21% 0.31 [-0.30, 0.91]
Schmidt et al (2016) [44] 3.74% -0.46 [-1.18, 0.27]
Uher et al (2014) [45] 20.14% -0.10 [-0.36, 0.16]
Dome et al (2012) [46] 1.97% -0.22 [-1.23, 0.80]
Chang et al (2012) [47] 14.63% 0.24 [-0.09, 0.56]
Harley et al (2010) [48] 13.12% -0.24 [-0.59, 0.11]
Lanquillon et al (2000) [11] 3.03% 0.00 [-0.81, 0.81]
RE Model 100% -0.13 [-0.28, 0.01]
Lower in responder
Higher in responder
-1.5 -1 -0.5 0 0.5 1
Difference of baseline CRP levels, SMD
Standard Error
0 0.129 0.259 0.388 0.518
-1 -0.5 0 0.5 1
Standardized Mean Difference

c

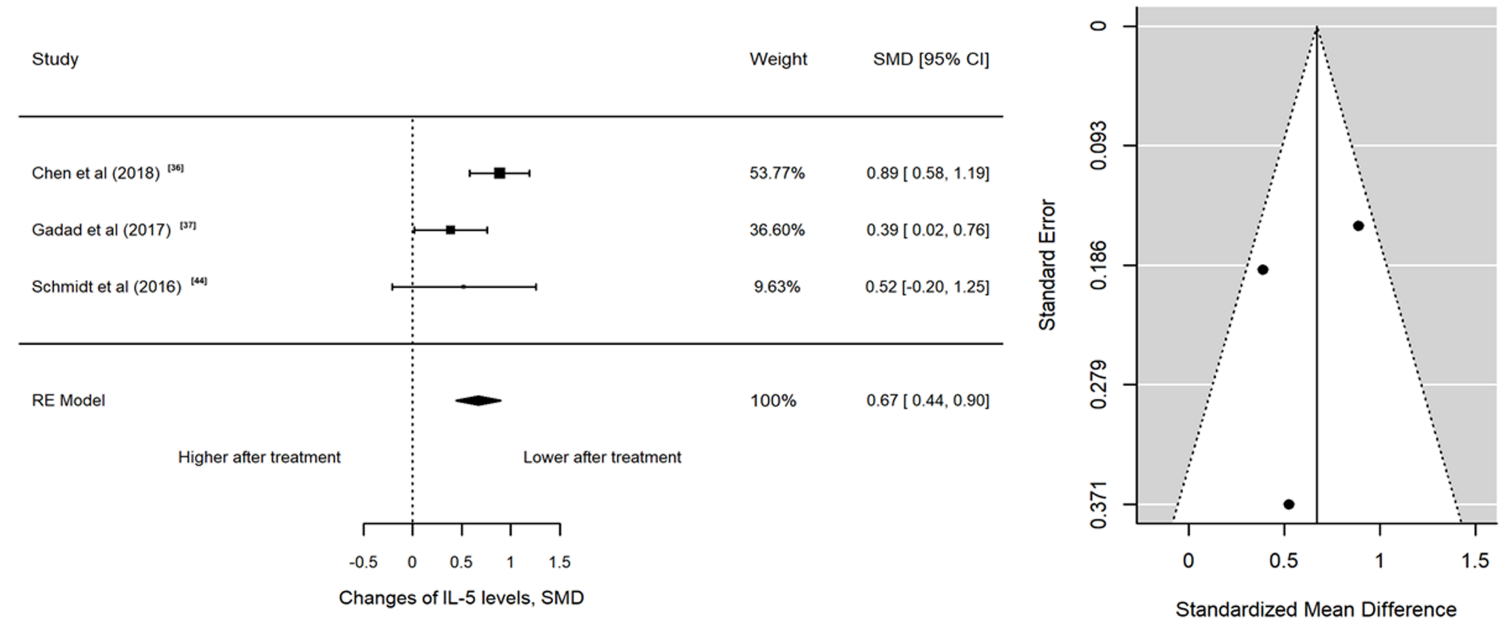

Baseline IL-6 levels and treatment response
Study
Weight
SMD [95% CI]
El-Haggar et al (2018) [49] 5.4% -0.37 [-1.01, 0.28]
Brunoni et al (2018) [35] 5.5% -0.21 [-0.63, 0.22]
Ricken et al (2018) [33] 5.5% -0.23 [-0.64, 0.18]
Reininghaus et al (2018) [31] 5.5% 0.18 [-0.25, 0.60]
Chen et al (2018) [36] 5.5% -0.10 [-0.39, 0.19]
Hasebe et al (2017) [34] 5.5% -0.48 [-0.90, -0.06]
Lindqvist et al (2017) [42] 5.2% 0.03 [-0.83, 0.90]
Gadad et al (2017) [37] 5.5% 0.09 [-0.33, 0.52]
Ormstad et al (2016) [38] 5.4% 0.27 [-0.34, 0.87]
Muthuramalingam et al (2016) [50] 5.3% 0.14 [-0.61, 0.89]
Manoharan et al (2016) [51] 5.5% 0.00 [-0.46, 0.46]
Liu et al (2015) [57] 5.3% -0.17 [-0.94, 0.59]
Brunoni et al (2014) [52] 5.1% -0.49 [-1.55, 0.57]
Yoshimura et al (2013) [55] 5.5% 0.11 [-0.24, 0.46]
Fornaro et al (2011) [53] 5.1% -0.61 [-1.62, 0.40]
Sun et al (2010) [56] 5.3% -0.02 [-0.79, 0.76]
Basterzi et al (2005) [54] 5.1% 1.00 [0.03, 1.98]
Mikova et al (2001) [41] 5.0% -0.66 [-1.78, 0.46]
Lanquillon et al (2000) [11] 3.8% -7.57 [-9.86, -5.28]
RE Model 100% -0.37 [-1.15, 0.42]
Lower in responder
Higher in responder
-10 -5 0 5
Difference of baseline IL-6 levels, SMD
Standard Error
0 0.292 0.584 0.876 1.169
-8 -6 -4 -2 0 2
Standardized Mean Difference

a


Antidepressant treatment effect on TNF-α level changes in responders
Study
Weight
SMD [95% CI]
El-Haggar et al (2018) [49] 3.25% 3.02 [2.16, 3.89]
Brunoni et al (2018) [35] 3.84% -0.27 [-0.70, 0.17]
Ricken et al (2018) [33] 3.86% -0.07 [-0.50, 0.35]
Chen et al (2018) [36] 3.98% 0.12 [-0.17, 0.41]
Lindqvist et al (2017) [42] 3.32% 0.07 [-0.75, 0.89]
Gadad et al (2017) [37] 3.91% -0.22 [-0.58, 0.15]
Gupta et al (2017) [58] 3.87% 1.33 [0.92, 1.75]
Gupta et al (2016) [59] 3.64% 1.16 [0.56, 1.76]
Myung et al (2016) [39] 3.84% 0.03 [-0.41, 0.46]
Ormstad et al (2016) [38] 3.68% 0.48 [-0.09, 1.05]
Muthuramalingam et al (2016) [50] 3.13% 1.48 [0.54, 2.42]
Schmidt et al (2016) [44] 3.46% 0.46 [-0.26, 1.19]
Brunoni et al (2014) [52] 2.96% -0.11 [-1.16, 0.93]
Zoga et al (2014) [24] 3.84% 0.20 [-0.24, 0.64]
Huang et al (2014) [63] 3.74% -0.18 [-0.71, 0.34]
Fornaro et al (2013) [60] 3.22% 1.34 [0.46, 2.23]
Li et al (2013) [61] 3.78% 2.06 [1.57, 2.55]
Dome et al (2012) [46] 3.23% -0.06 [-0.94, 0.81]
Sun et al (2010) [56] 3.57% 0.16 [-0.50, 0.81]
Yoshimura et al (2009) [10] 3.77% 0.28 [-0.22, 0.78]
Eller et al (2009) [40] 3.57% -0.17 [-0.82, 0.49]
Piletz et al (2009) [25] 3.47% 0.63 [-0.09, 1.35]
Eller et al (2008) [32] 3.95% -0.12 [-0.44, 0.20]
Sutcigil et al (2007) [8] 3.52% 1.82 [1.13, 2.51]
Himmerich et al (2006) [62] 3.79% 0.01 [-0.47, 0.50]
Tuglu et al (2003) [26] 3.59% 1.73 [1.10, 2.37]
Mikova et al (2001) [41] 3.15% -0.18 [-1.11, 0.74]
Lanquillon et al (2000) [11] 3.06% 2.48 [1.49, 3.46]
RE Model 100% 0.60 [0.26, 0.94]
Higher after treatment
Lower after treatment
-2 -1 0 1 2 3 4
Changes of TNF-α levels, SMD

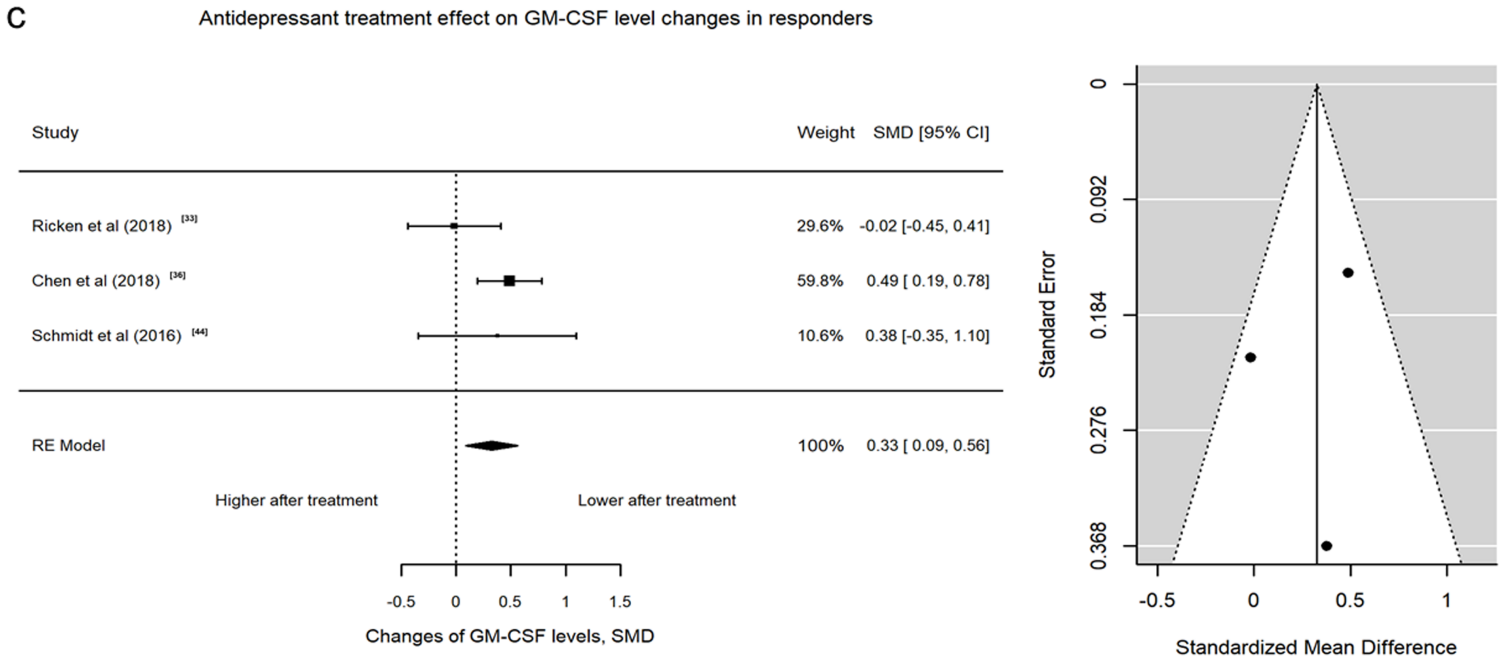
Standard Error
0
0.134
0.267
0.401
0.535
0 1 2 3
Standardized Mean Difference

b


Antidepressant treatment effect on IL-5 level changes in responders
Study
Weight
SMD [95% CI]
Chen et al (2018) [36] 53.77% 0.89 [0.58, 1.19]
Gadad et al (2017) [37] 36.60% 0.39 [0.02, 0.76]
Schmidt et al (2016) [44] 9.63% 0.52 [-0.20, 1.25]
RE Model 100% 0.67 [0.44, 0.90]
Higher after treatment
Lower after treatment
-0.5 0 0.5 1 1.5
Changes of IL-5 levels, SMD

Standard Error
0
0.093
0.186
0.279
0.371
0 0.5 1 1.5
Standardized Mean Difference

c


Antidepressant treatment effect on GM-CSF level changes in responders
Study
Weight
SMD [95% CI]
Ricken et al (2018) [33] 29.6% -0.02 [-0.45, 0.41]
Chen et al (2018) [36] 59.8% 0.49 [0.19, 0.78]
Schmidt et al (2016) [44] 10.6% 0.38 [-0.35, 1.10]
RE Model 100% 0.33 [0.09, 0.56]
Higher after treatment
Lower after treatment
-0.5 0 0.5 1 1.5
Changes of GM-CSF levels, SMD

Standard Error
0
0.092
0.184
0.276
0.368
-0.5 0 0.5 1
Standardized Mean Difference

Table 1. Primary meta-analyses of studies measuring baseline peripheral cytokines in antidepressant responders and non-responders.

Cytokines	Responders (*N*)	Non-responders (*N*)	ES (95% CI)	P-value	I^2 (%)	P-value Egger's test
IL-1β	227	239	-0.08 (-0.46, 0.30)	0.67	70.25	0.09
IL-2	168	186	0.08 (-0.29, 0.45)	0.67	56.01	0.28
IL-4	232	260	-0.15 (-0.34, 0.02)	0.09	0	0.30
IL-5	163	143	-0.13 (-0.55, 0.29)	0.54	62.46	0.43
IL-6	565	561	-0.91 (-1.15, 0.42)	0.36	97.49	0.10
IL-8	397	311	-0.28 (-0.43, -0.13)	**0.0003**	0	0.20
IL-10	237	283	-0.05 (-0.36, 0.27)	0.78	61.37	0.87
IL-12	68	79	0.09 (-0.32, 0.50)	0.67	29.30	0.69
TNF-α	738	517	-0.06 (-0.19, 0.06)	0.33	11.97	0.06
IFNγ	223	221	-0.10 (-0.29, 0.09)	0.29	0	0.13
GM-CSF	148	158	0.03 (-0.23, 0.29)	0.84	17.05	0.03
CRP	518	454	-0.13 (-0.28, 0.01)	0.07	15.59	0.96
MIP-1α	112	72	-0.16 (-0.75, 0.43)	0.59	71.76	0.60
Eotaxin-1	128	79	-0.77 (-2.15, 0.61)	0.27	94.99	0.46

Table 2. Primary meta-analyses of studies measuring peripheral cytokines in MDD patients before and after antidepressant treatment.

Cytokines	**Responders**					**Non-responders**				
	N studies	ES (95% CI)	P-value	I^2 (%)	P-value Egger's test	N studies	ES (95% CI)	P-value	I^2 (%)	P-value Egger's test
TNF-α	28	0.60 (0.26, 0.94)	**0.0006**	90.98	**0.03**	24	0.14 (-0.07, 0.35)	0.18	59.09	0.32
IL-6	21	0.09 (-0.38, 0.56)	0.71	93.20	0.80	19	0.35 (-0.13, 0.83)	0.15	92.73	0.14
CRP	13	-0.06 (-0.34, 0.23)	0.70	75.59	0.46	11	0.04 (-0.47, 0.55)	0.88	88.01	0.10
IFNγ	10	-0.60 (-1.41, 0.21)	0.15	95.79	0.15	6	-0.002 (-0.42, 0.42)	0.99	75.07	0.20
IL-10	10	0.62 (-0.14, 1.38)	0.11	94.19	0.54	8	0.02 (-0.46, 0.50)	0.93	86.11	0.72
IL-1β	10	0.20 (-0.50, 0.91)	0.57	94.09	0.64	6	0.43 (-0.29, 1.15)	0.24	92.50	0.92
IL-8	9	-0.21 (-0.69, 0.26)	0.38	90.38	0.12	9	-0.08(-0.47, 0.31)	0.69	80.41	0.15
IL-4	9	-0.82 (-2.11, 0.48)	0.22	97.91	**0.02**	7	-0.57 (-1.98, 0.84)	0.42	98.02	**0.03**
IL-2	8	-0.11 (-1.19, 0.96)	0.84	96.38	0.55	5	-0.14 (-1.01, 0.73)	0.75	92.83	0.09
IL-12	4	0.28 (-0.05, 0.62)	0.10	0	0.40	3	-0.12 (-0.43, 0.19)	0.45	0	0.93
GM-CSF	3	0.33 (0.09, 0.56)	**0.007**	3.58	0.75	3	0.16 (-0.25, 0.54)	0.47	59.66	0.64
IL-5	3	0.67 (0.44, 0.90)	**<0.0001**	1.55	0.71	3	0.65 (0.02, 1.28)	**0.04**	80.71	0.35
MIP-1α	3	0.08 (-1.84, 0.34)	0.56	0	0.12	3	-0.65 (-1.73, 0.43)	0.24	88.78	0.41
Eotaxin-1	3	0.06 (-0.68, 0.81)	0.87	88.45	0.08	3	0.05 (-0.27, 0.36)	0.77	0	0.99